Homochirality

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The Origin of Stereoselectivity in Primary Amino Acid Catalyzed Intermolecular Aldol Reactions**

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The asymmetric amino acid catalyzed aldol reaction is plausibly an ancient transformation,[1] which enzymes have catalyzed for billions of years. These enzyme-catalyzed stereoselective aldol reactions involve enamine intermediates (type I aldolases) or zinc enolates (type II aldolases) as the reactive nucleophile.[2] The catalytic residue of type I aldolases is the primary amino group of a lysine moiety, which forms enamine intermediates with the help of a proton relay system by neighboring amino acids.[2c]

The ability of amino acids to catalyze the asymmetric aldol reaction was discovered in the 1970s by Hajos and Parrish[3] and Wiechert and co-workers,[4] and amino acid mediated stereoselective Robinson annulations were utilized numerous times in natural-product synthesis.[5] In 2000, List and co-workers demonstrated that proline and its derivatives can be used as catalysts for intermolecular asymmetric aldol reactions between ketones and aldehydes with moderate-to-excellent enantioselectivities.[6–7] Both the proline-catalyzed intramolecular and intermolecular aldol reactions involve an enamine mechanism, in which one proline molecule takes part in the transition state, as established by Houk, List, and co-workers.[8]

We recently found that acyclic amino acids and their derivatives are able to catalyze asymmetric intermolecular aldol reactions with high stereoselectivity.[1b,9] For example, simple natural and unnatural primary amino acid derivatives catalyzed the reaction between cyclohexanone **1** and an

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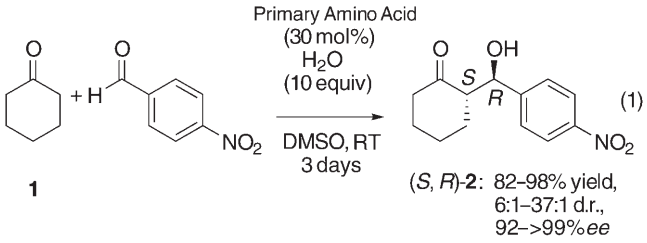
aldehyde in high yield and with up to >99% *ee* [Eq. (1); amino acid: (*S*)-alanine, (*S*)-aminobutyric acid, (*S*)-valine, (*S*)-asparatate, (*S*)-isoleucine, (*S*)-serine].[9]



Intrigued by the enzyme-like enantioselectivity of the acyclic amino acid catalyzed asymmetric aldol reaction, we became interested in unraveling the origins of its stereoselectivity. The origin of the stereoselectivity of acyclic amino acids is of great importance in understanding the origins of biological homochirality and the evolution of the catalytic mechanism of aldolase enzymes. In addition, the information gathered can aid the development of new organocatalysts.

Herein, we present how theoretical and experimental data can be combined to understand the stereochemistry of primary amino acid catalyzed intermolecular aldol reactions that involve enamine intermediates. We show that calculations provide key insight, not yet accessible by other means, into the mechanism and accurately predict the stereochemistry of the observed product.

We initially investigated the relationship between the enantiomeric excess of aldol product **2**, derived from the aldol reaction shown in Eq. (1), and the optical purity of the simplest chiral amino acid catalyst, (*S*)-alanine. Plotting the enantiomeric excess of alanine versus that of β-hydroxy ketone **2** showed a linear correlation (Figure 1).

Our results support the supposition that only one alanine molecule takes part in the transition state of the primary amino acid catalyzed asymmetric aldol reactions. This correlation together with previous theoretical findings by Houk and co-workers for proline-catalyzed aldol reactions[8] suggests that three possible mechanisms may describe the primary amino acid catalyzed asymmetric aldol reactions: the carboxylic acid catalyzed enamine mechanism, the amino catalyzed enamine mechanism, and the enaminium catalyzed mechanism (Scheme 1).

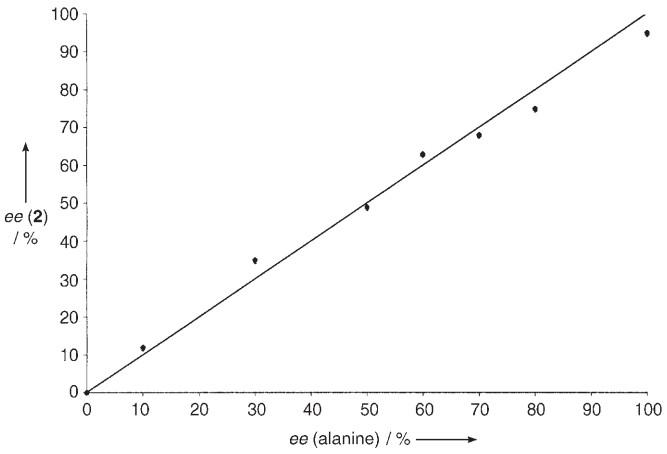
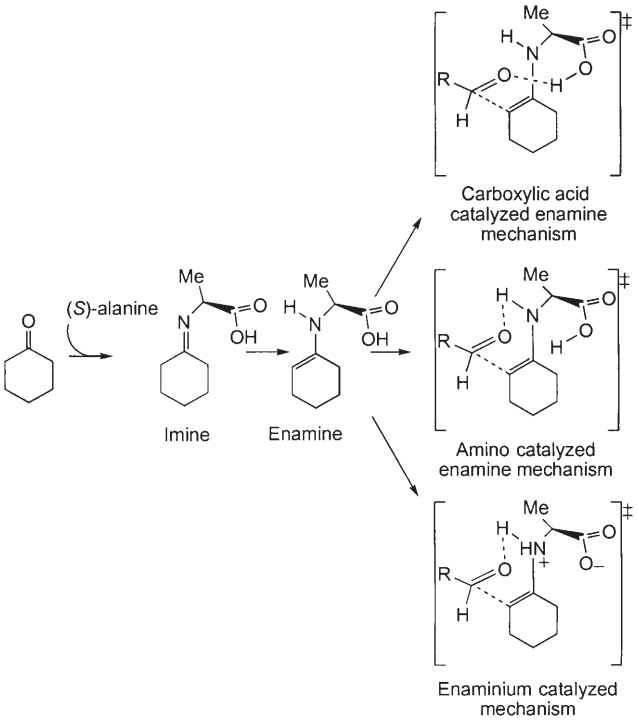


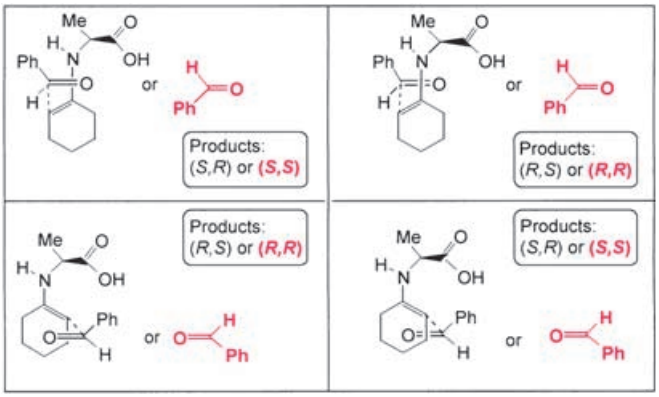
Figure 1. Relation between the enantiomeric excess of (*S*)-alanine and that of the aldol product **2** in the catalytic intermolecular asymmetric synthesis of **2**.



Scheme 1. The three possible mechanisms in the alanine-mediated aldol reaction which involve an enamine intermediate.

We then performed density functional theory (DFT) calculations on the alanine-catalyzed aldol reaction with **1** as the donor and benzaldehyde as the acceptor species. More specifically, we focused our attention on the nucleophilic attack of the enamine/enaminium moiety on the carbonyl group (see Scheme 1), as this step governs the configuration of the product, and located the possible transition-state structures associated with the C–C bond formation. Calculations indicate that the most accessible pathway corresponds to the enamine-catalyzed reaction, in which the C–C bond formation is coupled with proton transfer from the carboxylic group of the alanine moiety to the developing alkoxide (Scheme 1). Primary amino acids lead to an enamine intermediate that can rotate about the C_α–N bond in contrast to the corresponding proline-derived enamine intermediate, and thus more transition-state structures have to be envisioned. As shown in Scheme 2, different transition-state orientations that generate products with different configurations have been considered. For each of the eight orientations shown in Scheme 2, two possible proton-transfer arrangements have been studied together with two different conformations of the enamine ring, thus giving a total of 32 transition states. As an example, four transition-state structures that lead to the same *S*,*R* product are shown in Figure 2 (more transition-state structures are given in the Supporting Information).

Figure 3 shows the four transition-state structures that generate the four different stereoisomers with the lowest energy barriers. Among these four transition states, the one



Scheme 2. Transition-state arrangements that generate different diastereoisomers in the alanine-catalyzed aldol reaction between cyclohexanone and benzaldehyde.

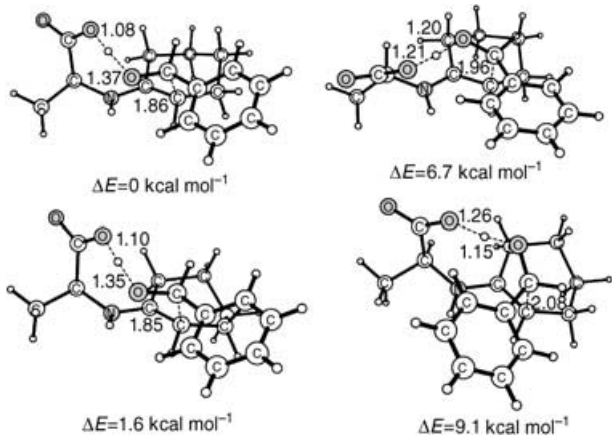


Figure 2. Four possible transition-state structures that generate the *S*,*R* product. They differ in the proton-transfer arrangement and the conformation of the enamine ring. Relative energies and relevant geometric parameters are shown (in Å).

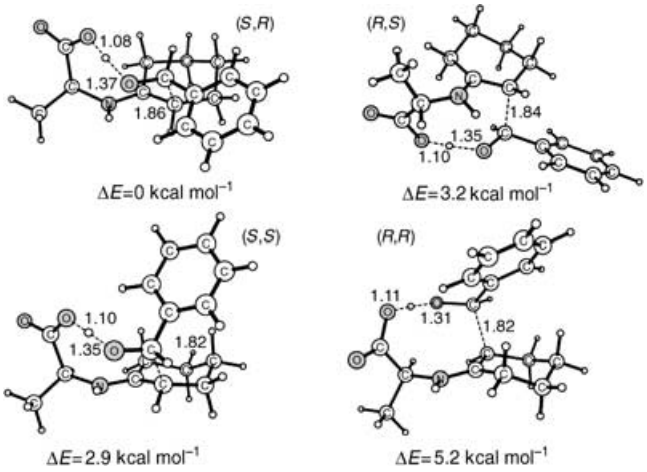


Figure 3. The energetically most accessible transition-state structures that lead to the four different diastereoisomers. Relative energies and relevant geometric parameters are shown (in Å).

that requires the lowest activation energy leads to the *S*,*R* enantiomer, which is indeed the product observed experimentally. The *R*,*S* enantiomer is formed through a transition-state structure that lies 3.2 kcal mol^{-1} higher in energy, which is in accordance with the experimental results (> 90 % *ee*).[9] The *S*,*S* enantiomer also requires a higher energy barrier (2.9 kcal mol^{-1}), thus explaining the high *anti* diastereoselectivity (d.r. > 10:1).

Scrutiny of the geometrical arrangements of the low-lying transition-state structures that lead to the different products (as shown in Figure 3) allows us to identify a few effects that contribute to the stereoselectivity of the reaction. First, it can be noticed that the electrostatic hydrogen-bonding interaction between the amino group and the developing alkoxide moiety plays an important role. The hydrogen bond (NH···O) is relatively short (about 2 Å) for the three lowest transition-state structures in Figure 3 (those that lead to the *S*,*R*-, *R*,*S*-, and *S*,*S*-enantiomeric products). This hydrogen-bonding interaction is absent in the transition-state structure that leads to the *R*,*R* product and in general in most of the transition-state structures with higher energies (see the Supporting Information). Another factor that regulates the stereoselectivity is the steric repulsion between the phenyl and cyclohexyl rings in the transition state. Accordingly, the eclipsed conformation of the phenyl and cyclohexyl rings in the transition state that leads to the *S*,*S* product results in higher energy relative to the *S*,*R* transition state, in which the two rings are in a staggered conformation instead. Finally, the methyl substituent of (*S*)-alanine interacts unfavorably with the cyclohexyl ring, thus leading to the higher energy of the *R*,*S* transition state relative to the *S*,*R* structure, in which the methyl group points away from the cyclohexyl moiety. The interplay between these effects ultimately determines the relative energies of the various transition states and, thus, drives the stereoselectivity of the primary amino acid catalyzed intermolecular aldol reaction.

The energy diagram associated with the formation of the observed product, the *S*,*R* enantiomer (see Figure 4), shows that the nucleophilic attack is slightly endothermic and, thus, reversible.

The other two mechanisms investigated herein, the enaminium- and the amino-catalyzed mechanisms, are presented in Scheme 1. In the calculations that involve zwitterionic-like structures, geometric optimizations in a dielectric

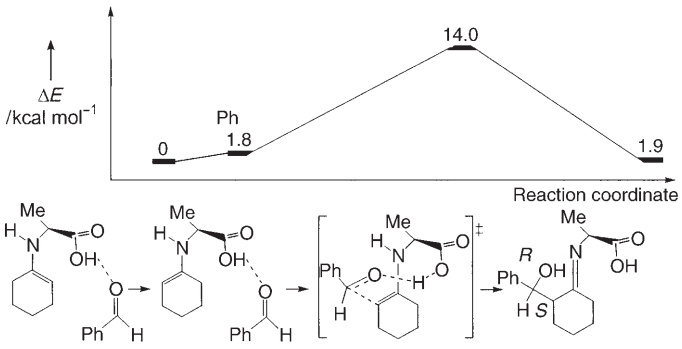
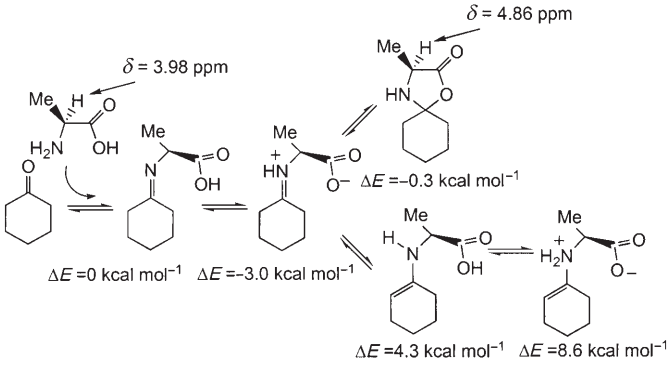


Figure 4. The energy diagram associated with the formation of the *S*,*R* product. For convenience, the neutral intermediate, and not the zwitterionic-type structure, has been optimized.

continuum medium were necessary to fully optimize the transition-state structures (more details of the calculations are described in the Experimental Section). The two alternative mechanisms require activation energies much higher than the corresponding energies of the carboxylic acid catalyzed enamine mechanism at the same level of theory (see details in the Supporting Information). The higher energy barriers, as found by computation (higher than 15 kcal mol^{-1}, as described in the Supporting Information), allow us to safely dismiss the enaminium- as well as the amino-catalyzed mechanisms in the alanine-catalyzed aldol reaction and, by extension, for the other primary amino acids as well.

The acyclic amino acid catalyzed aldol reaction is significantly accelerated by a small amount of water.[9] We therefore performed NMR spectroscopic analysis according to List et al.[7j] to reveal the possible presence of oxazolidinone intermediates formed between the ketone donor and alanine, which would thus reduce the enamine concentration and lead to a decrease in the reaction rate (Scheme 3). The



Scheme 3. Relative energies of different intermediates and of the oxazolidinone inhibitor in the alanine-mediated aldol reaction occurring by an enamine pathway.

formation of the oxazolidinone was indicated by a change in the chemical shift of the α proton of alanine from $\delta = 3.98$ to 4.86 ppm. In addition, calculations were made to shed light on the NMR spectral data. The computed relative energies of the imine, iminium, enamine, enaminium, and oxazolidinone moieties show that the formation of oxazolidinone from the imine functionality is a slightly exothermic and, thus, more favorable process (see Scheme 3). Moreover, the oxazolidinone lies lower in energy than the enamine, which is the reactive nucleophile in the aldol reaction. Hence, the competing oxazolidinone reaction may explain why the primary amino acid catalyzed aldol reactions are very slow in the absence of a few equivalents of water.[9]

In summary, our DFT calculations, supported by additional experimental data, provide a key basis for understanding primary amino acid intermolecular aldol reactions in which only one amino acid molecule is involved in the transition state. We showed for alanine that the carboxylic acid catalyzed enamine mechanism is more favorable than other mechanisms because it requires the lowest activation energy. Furthermore, the calculations demonstrate that such a mechanism accurately predicts the proper stereochemistry of the reaction.

Experimental Section

All ground-state and transition-state geometries were optimized by using hybrid density functional theory[10] and a standard double zeta plus polarization basis set (B3LYP/6-31G(d,p)) with the Gaussian03 software package.[11] Final energies for the fully optimized structures were obtained by using the larger basis set 6-311 + (2d,2p) and were corrected for zero-point effects derived from frequency analysis at the B3LYP/6-31G(d,p) level of theory. When zwitterionic-like structures were involved, geometry optimizations and frequency calculations were performed in the presence of a solvent by using the CPCM polarizable conductor calculation model ($\varepsilon = 36.5$);[12] the radii derived from the UFF force field were employed to build the cavity. This procedure was adopted in the evaluation of the energies of the imine, iminium, enamine, enaminium, and oxazolidinone moieties (Scheme 3), and in the investigation of the enaminium-catalyzed mechanism (see the Supporting Information); for comparison, it was also used for the amino-catalyzed enamine mechanism. To test the solvent effects in the carboxylic acid catalyzed enamine mechanism and to compare the energies of the three different mechanisms, three transition-state structures from the carboxylic acid catalyzed enamine mechanism (those with the lowest energy barrier) were reoptimized in the presence of the solvent. Their relative energies were not significantly affected by the different optimization procedure (see Figure 3 and the Supporting Information).

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